B6-Trex1 KO

Strain Name: *C57B6/JGpt-Trex1 em1Cd1194 /Gpt*

Strain type: Knock-out

Strain ID: T013987

Background: B6/JGpt

Description

TREX1 (DNase III) is the major 3′ -5′ DNA exonuclease in mammalian cells and plays a primary role in cell death and genomic DNA degradation [1]. Dysfunction of Trex1 may lead to the accumulation of DNA, thereby activating the autoimmune response. Trex1-knockout mice develop inflammatory myocarditis similar to autoimmune cardiomyopathy and produce type 1 interferon [2]. Additionally, the TREX1 D18N point mutation causes familial chilblain lupus, a monogenic cutaneous lupus. Meanwhile, the TREX1 D18N point mutation results in a double-stranded DNA degradation disorder, demonstrating the association between double-stranded DNA degradation and nucleic acid-mediated autoimmune diseases.

GemPharmatech has developed *Trex1*$^{-/-}$ mice and conducted phenotypic analysis. These mice show an increase in the level of anti-dsDNA in the serum and present multi-organ inflammatory phenotypes. This model can be used to evaluate the potential pathogenic mechanisms of Trex1-related signaling pathways in systemic lupus erythematosus, providing a useful tool for studying the pathogenesis of Trex1-mediated autoimmune diseases and evaluating potential treatment options for lupus

Strategy

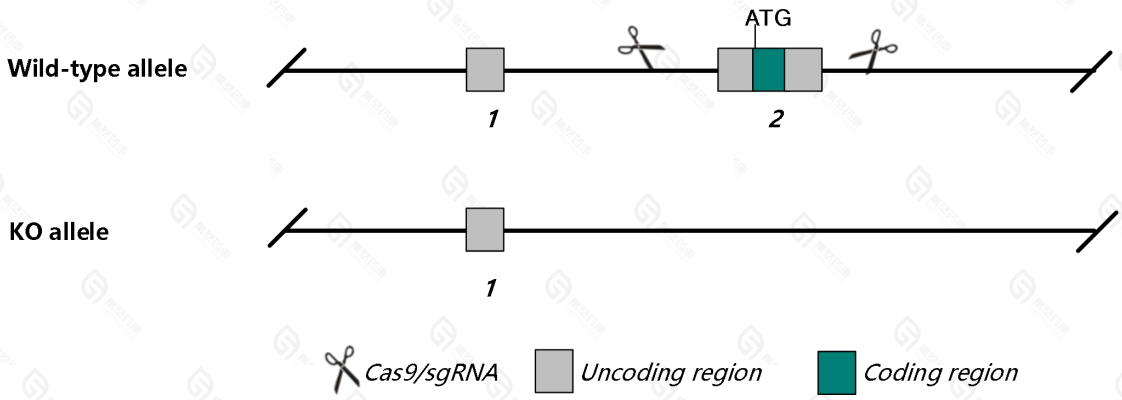


Fig.1 Schematic diagram of B6-Trex1 ko mice.

Application

1. Research on the pathogenesis of Systemic Lupus Erythematosus
2. Screening of therapeutic drugs for Systemic Lupus Erythematosus and efficacy trials
3. Research related to the immune system

Data support

1. Analysis of TERX1 expression

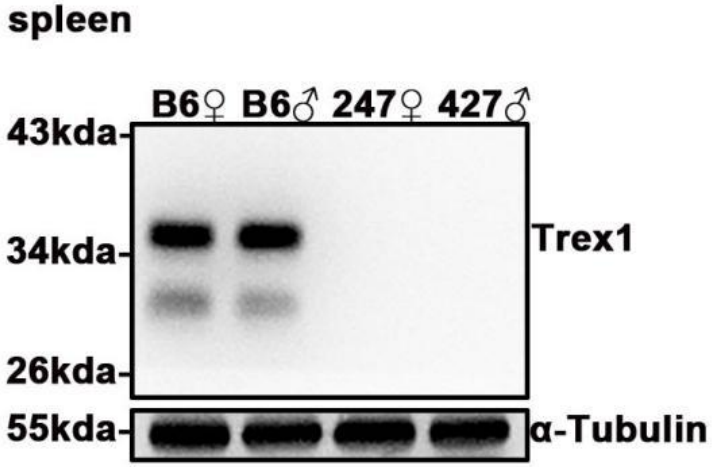


Fig.2 Analysis of TREX1 protein expression

Collect the spleens of wildtipe B6 and Trex1 KO mice, and detect the expression of TREX1 protein by Western blot. The expression of TREX1 protein can be only detected in wildtype B6 mice. In the spleens of B6 Trex1 KO mice, the expression of TREX1 is absent, demonstrating the successful knockout of Trex1 in this mouse model..

2. Observation of the survival rate of B6-Trex1 KO mice.

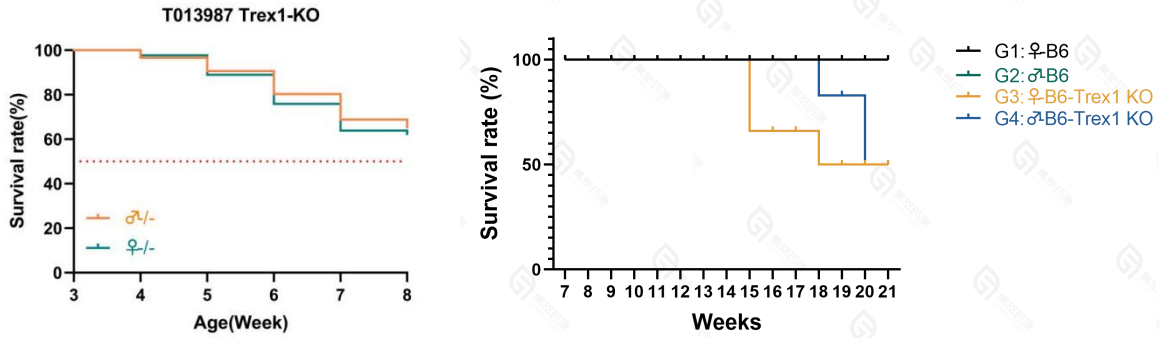


Fig.3 Survival Curve of B6-Trex1 KO Mice.

The survival rate of B6-Trex1 KO mice aged 3 - 8 weeks was observed. The results showed that both female and male B6-Trex1 KO mice had a certain mortality rate from 4 weeks to 7 weeks of age (Fig.3 left), and also from 15 - 20 weeks of age(Fig.3 right).
Note: For the evaluation of the efficacy of drugs on the survival rate index using this model, it is recommended to select mice at 3 weeks of age for the experiment. If evaluating the efficacy of drugs on other indicators of the SLE model, it is advisable to choose mice with a relatively larger body weight at 4 - 5 weeks of age for the experiment.

3. Detection of anti-dsDNA antibody levels

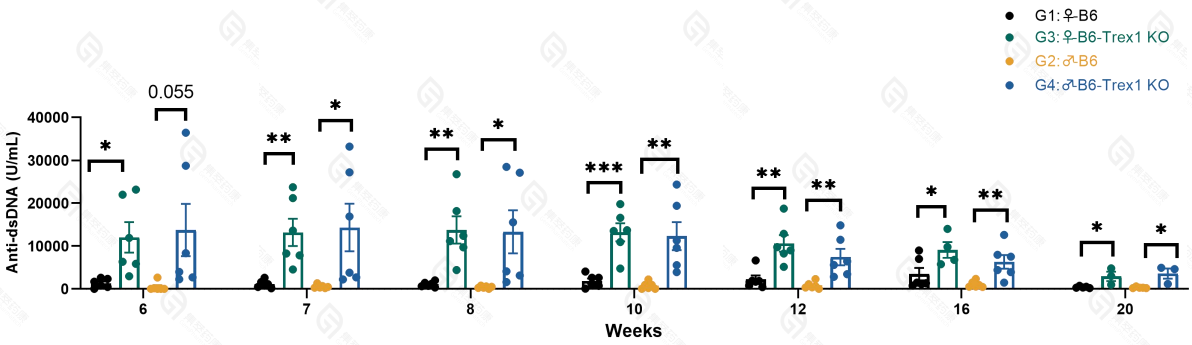
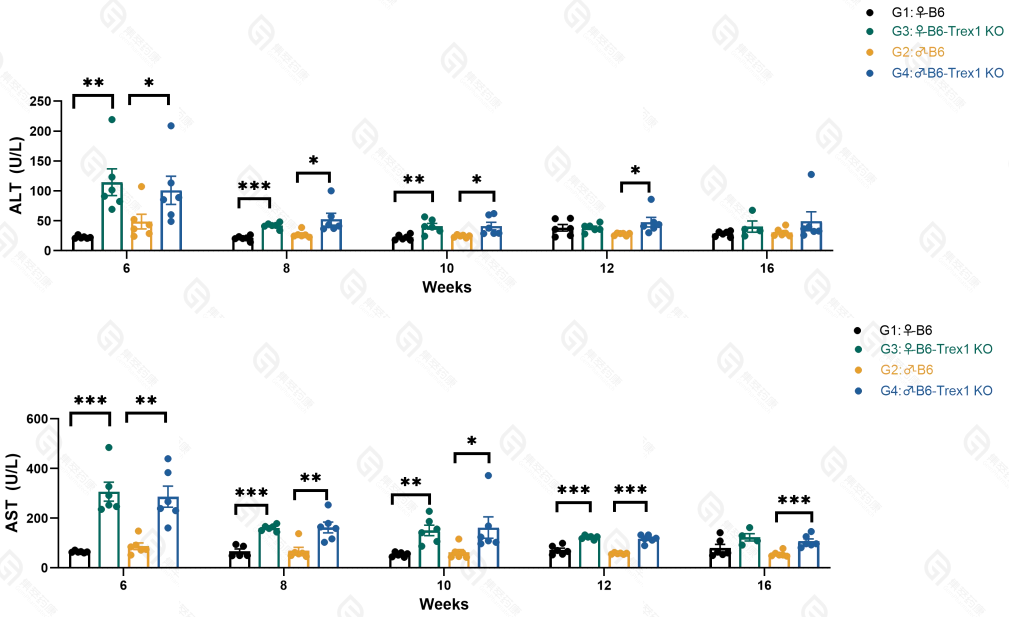


Fig.4 Detection of anti-dsDNA antibody levels in B6-Trex1 KO Mice Aged 6 - 20 weeks

The levels of anti-dsDNA IgG antibody in the serum were detected in wild-type mice and B6 Trex1-KO mice respectively. In both female and male mice aged 6 to 20 weeks, the level of anti-dsDNA antibodies in the serum of B6 Trex1-KO mice was significantly higher than that in the control wild-type mice.

4. Blood biochemical test



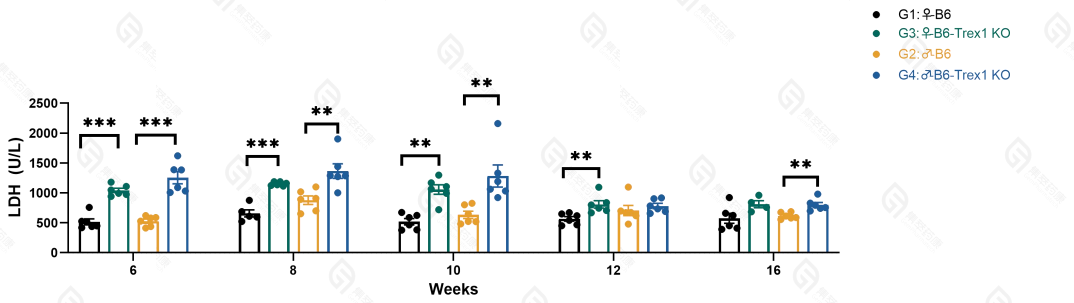


Fig.5 Blood biochemical test

The levels of ALT, AST, and LDH in the serum of 6 - 18 week old female and male B6 Trex1 KO mice were higher than those of the corresponding female and male control mice respectively. This indicates that the livers and hearts of the mice have suffered a certain degree of damage.

5. Pathological examination

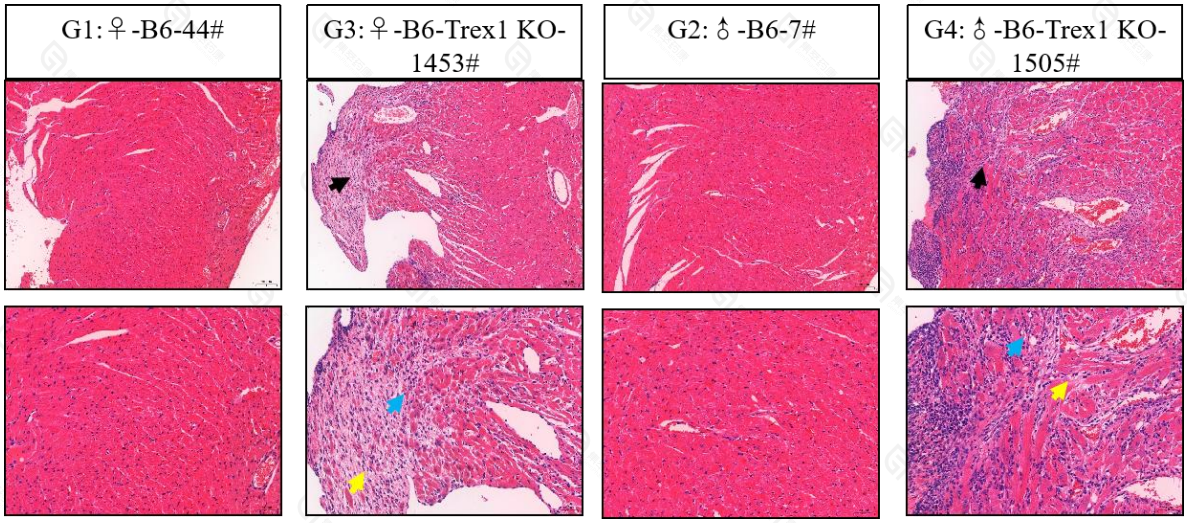
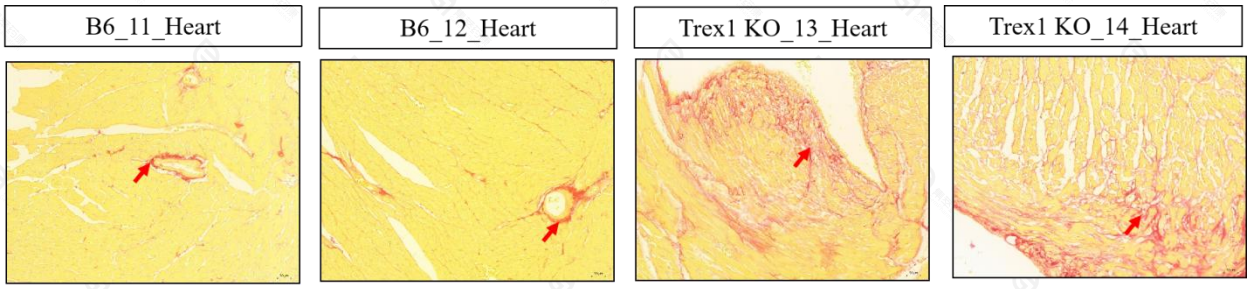


Fig.6 HE Pathological staining analysis of the hearts of 21 week old B6-Trex1 KO Mice

Collect heart tissues from 21 week old wildtype mice and B6-Trex1KO mice for HE pathological staining section analysis. The results show myocardial fiber degeneration and necrosis (black arrow), lymphocytes (blue arrow), and fibrous tissue hyperplasia (yellow arrow) in the B6-Trex1KO mice.

6. **Pathological examination of tissue fibrosis**



Sirian Red staining of heart tissue: Fiber expression (red arrow) Bar=50 μm

Fig.7 Sirius Red pathological staining analysis of the heart of 13 week old B6-Trex1 KO Mice

Collect heart tissues from 13 week old wildtype mice and B6-Trex1KO mice for Sirius Red pathological staining section analysis. The results show heart fiber expression (Red arrow) in the B6-Trex1KO mice

7. **Detection of interferon-stimulated DNA (ISD) response in tissues of 32-week-old mice**

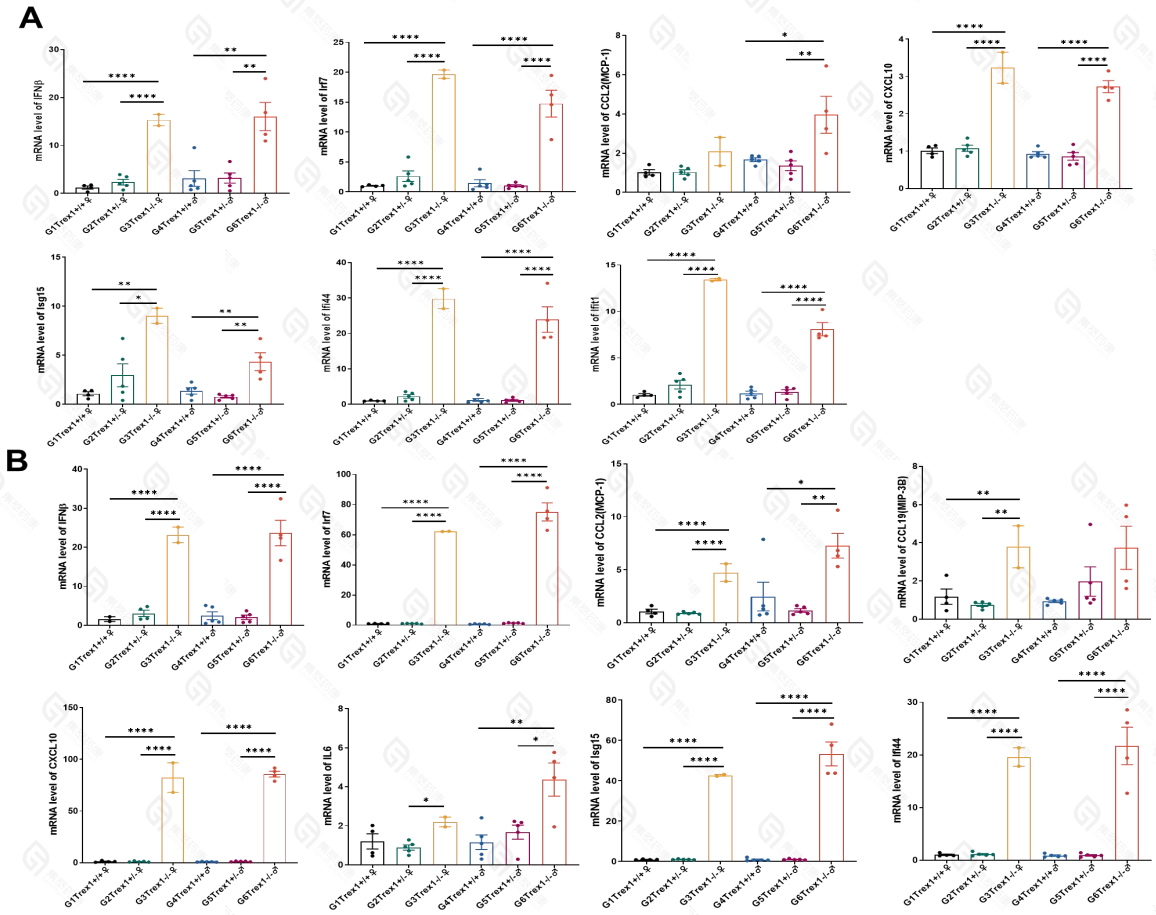


Fig.8 Detection of Interferon-stimulated DNA (ISD) response in spleen and heart tissues of 32 week old B6-Trex1 KO Mice

Spleen and heart tissues were taken from 32 week old wild-type mice and B6-Trex1 KO mice. The expression levels of interferon-stimulated DNA response (ISD) genes were detected using Q-PCR test. The expression of ISD in the spleen (A) and heart (B) of Trex1 KO mice was significantly higher than that in the control mice.

8. In vivo pharmacodynamic experiment

Detection of survival rate

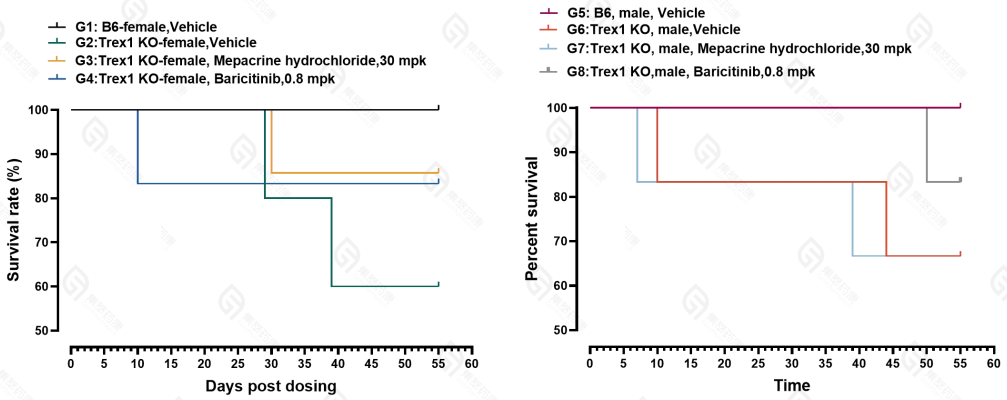


Fig.9 Survival Rate after Drug Treatment

Trex1 KO mice were treated with Mepacrine hydrochloride (an antimalarial drug) and Baricitinib (a JAK1/2 inhibitor). The natural mortality rate of Trex1 KO mice in the drug treated group was significantly lower than that in the untreated group.

Detection of anti-dsDNA antibody levels

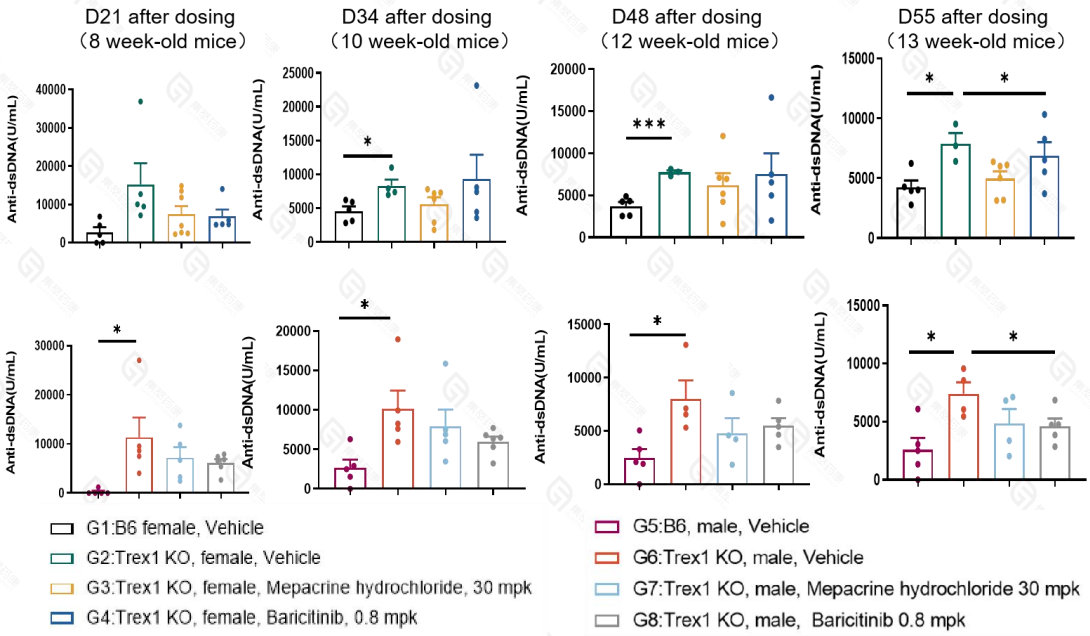


Fig.10 Detection of anti-dsDNA antibody levels in serum

The Baricitinib-treated group exhibited a reduction in the serum anti-dsDNA levels of

Trex1-KO mice. The Mepacrine hydrochloride treated group also demonstrated therapeutic effects.

Blood biochemical test

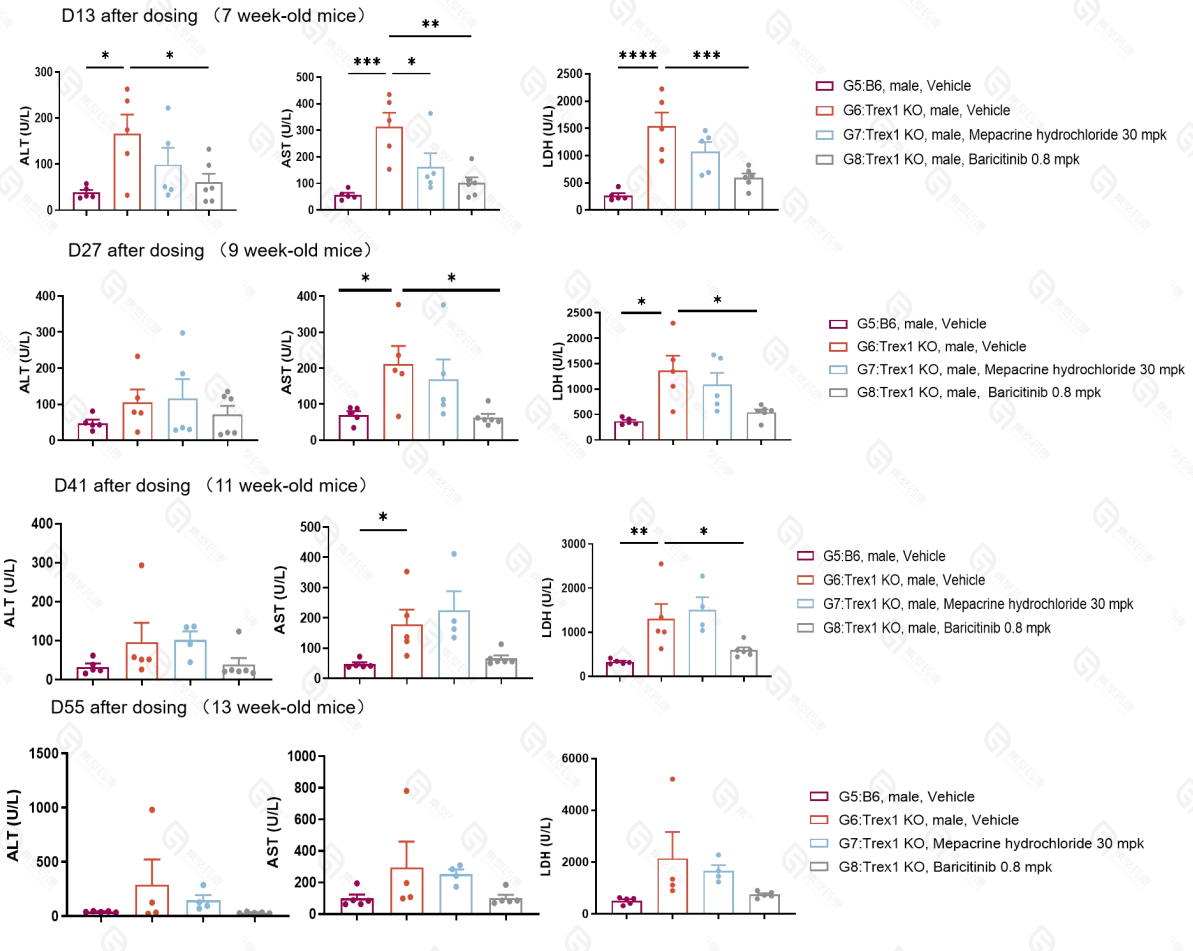


Fig.11 Blood biochemical test

Blood biochemical tests were conducted to analyze the ALT, AST, and LDH indices. The Baricitinib treated group decreased the serum levels of ALT, AST, and LDH in Trex1-KO mice. The Mepacrine hydrochloride treated group also showed therapeutic effects.

Histochemical detection

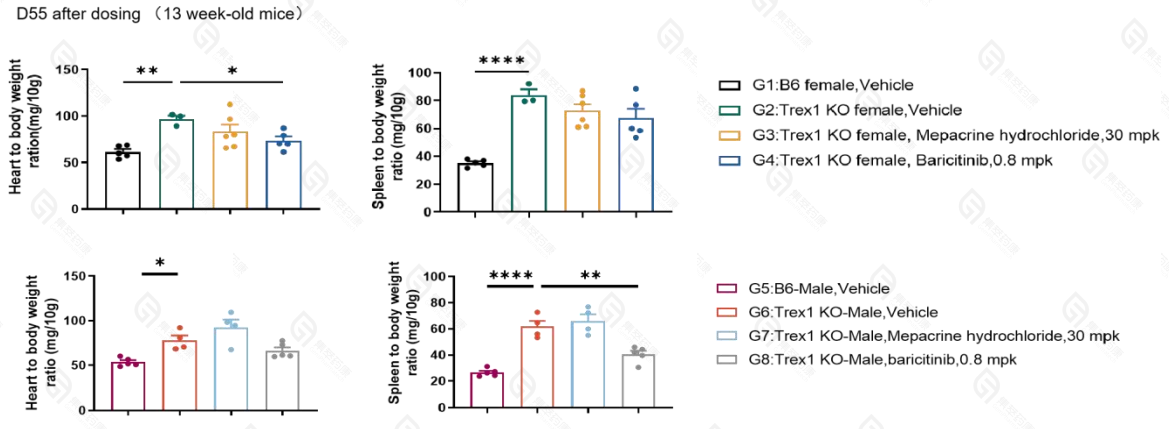


Fig.12 Ratio of heart and spleen weight to body weight

The spleen and heart tissues of Trex1-KO mice became enlarged, and the drug treatment group could alleviate this phenotype.

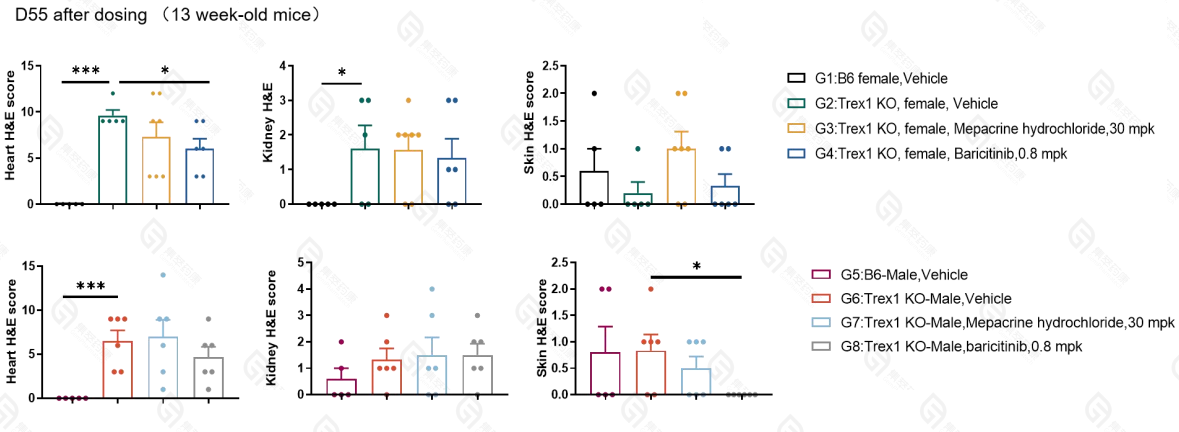


Fig.13 Pathological Score of Heart, Kidney and Skin

Trex1 KO mice exhibited obvious pathological changes in the heart, kidney and skin tissue. Treatment with Baricitinib could alleviate these pathological changes.

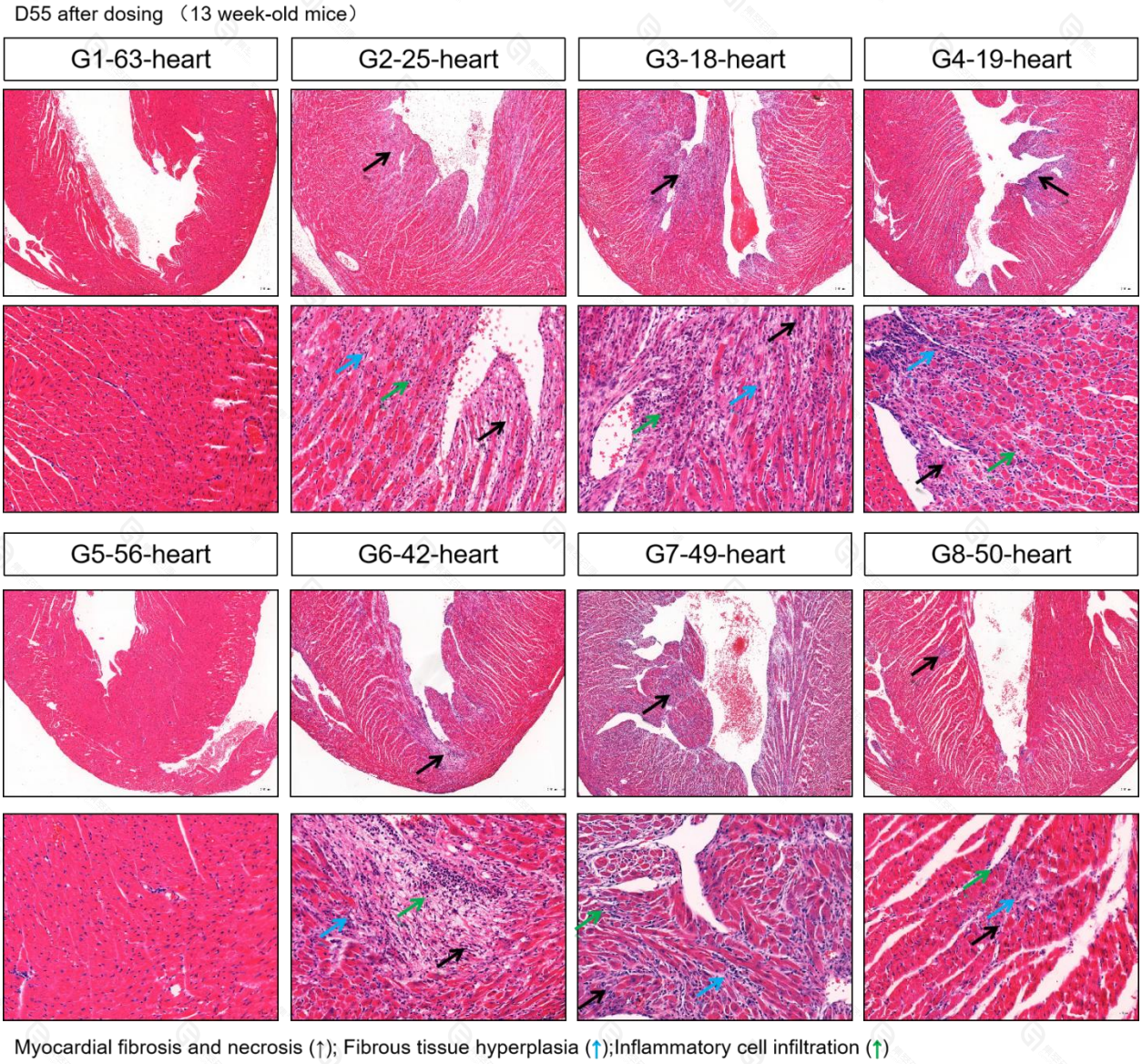


Fig.14 Pathology of Heart

Heart tissues were collected for pathological examination. Myocardial fibrosis and necrosis (black arrows); Fibrous tissue hyperplasia (blue arrows); Inflammatory cell infiltration (green arrows).

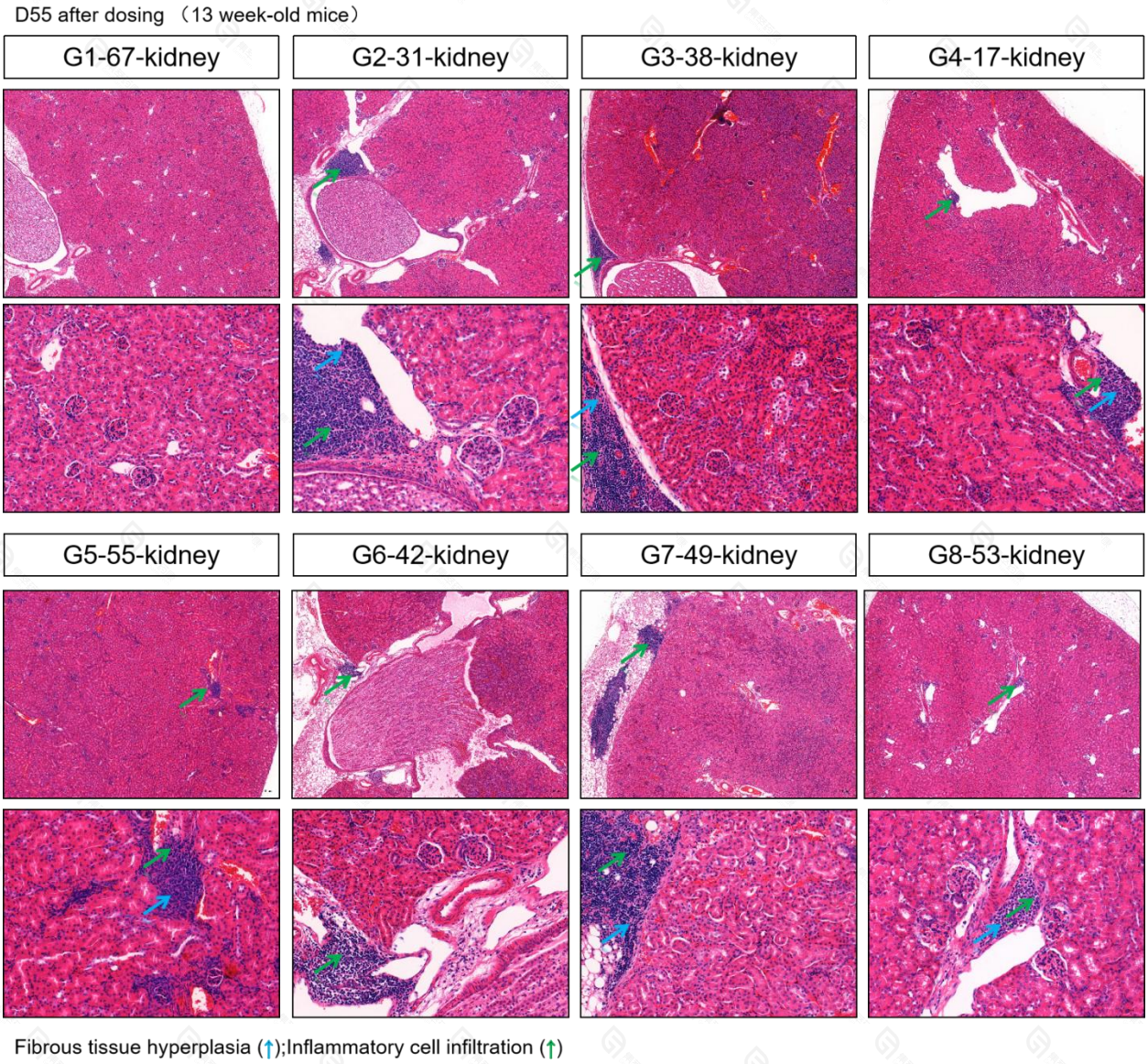


Fig.15 Pathology of Kidney

Kidney tissues were collected for pathological examination. Fibrous tissue hyperplasia (blue arrows); Inflammatory cell infiltration (green arrows)

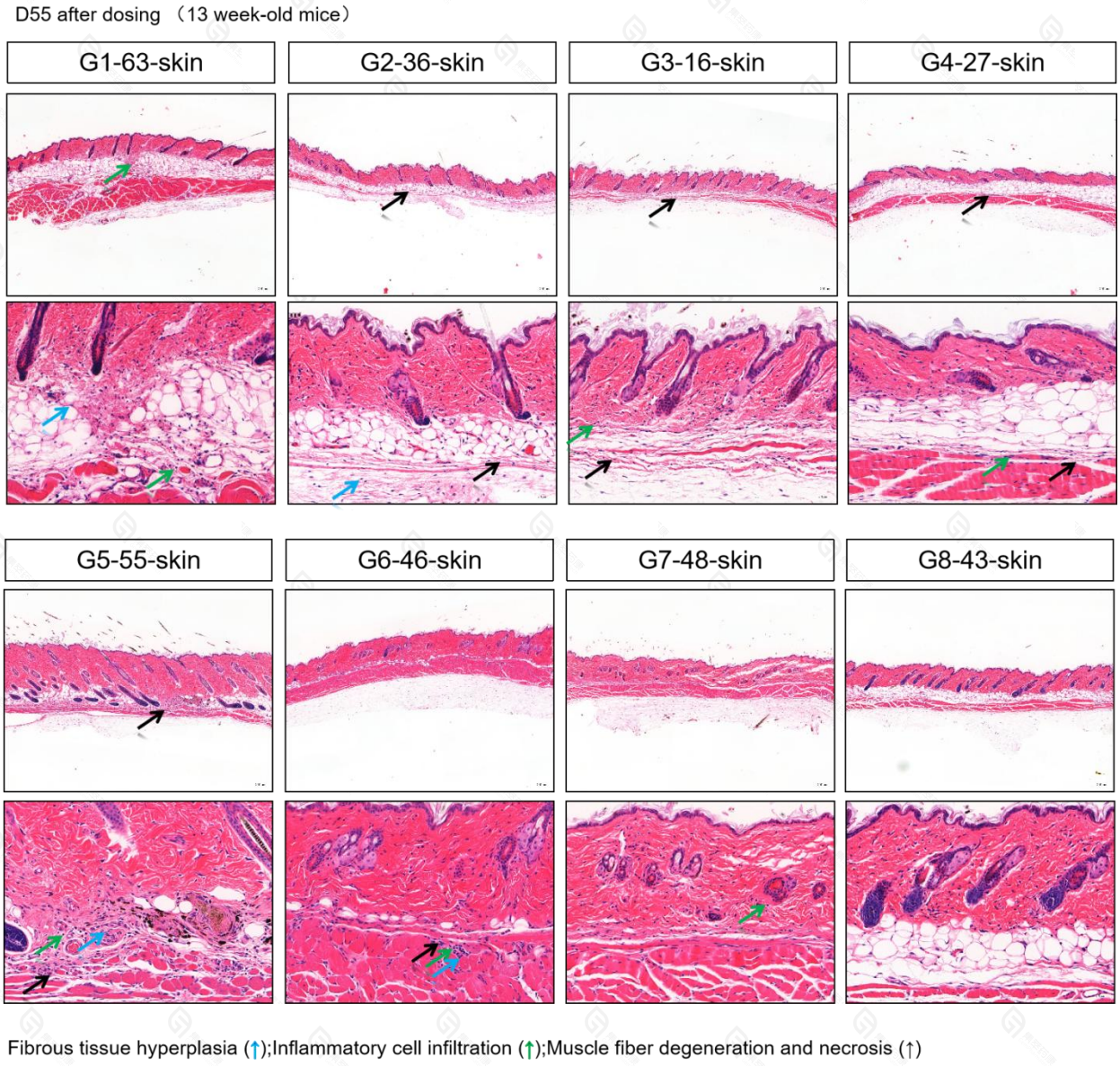


Fig.16 Pathology of Skin

Skin tissues were collected for pathological examination. Fibrous tissue hyperplasia (blue arrows); Inflammatory cell infiltration (green arrows);Muscle fiber degeneration and necrosis (black arrow)

References

1. Mazur DJ, Perrino FW. Structure and expression of the TREX1 and TREX2 3' --> 5'

exonuclease genes. J Biol Chem. 2001 May 4;276(18):14718-27.

2. Lee-Kirsch MA, et al.Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nat Genet. 2007 Sep;39(9):1065-7.

3. Grieves JL, Fye JM, Harvey S, Grayson JM, Hollis T, Perrino FW. Exonuclease TREX1 degrades double-stranded DNA to prevent spontaneous lupus-like inflammatory disease. Proc Natl Acad Sci U S A. 2015 Apr 21;112(16):5117-22